

# Predictors of non-functional larynx following (chemo)radiotherapy for locally advanced laryngeal cancer

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## Abstract

\* Non-functional larynx (NFL) was found to affect 30.9 % of patients with locally advanced laryngeal cancer who underwent curative non-surgical laryngeal preservation treatment for stage III/IV disease \* The key measures of NFL were long-term gastrostomy and tracheostomy dependence, functional laryngectomy and chronic aspiration. \* Multivariate analyses identified current smoking to be associated with 6.8-fold increase in NFL \* Patients with pre-treatment hemi-laryngeal fixation were 3.4 times more likely to experience locoregional recurrence.

## KEY POINTS

- Non-functional larynx (NFL) was found to affect 30.9 % of patients with locally advanced laryngeal cancer who underwent curative non-surgical treatment
- The key measures of NFL were long-term gastrostomy and tracheostomy dependence, functional laryngectomy and chronic aspiration.
- Multivariate analyses identified current smoking to be associated with 6.8-fold increase in NFL
- Patients with pre-treatment hemi-laryngeal fixation were 3.4 times more likely to experience locoregional recurrence.
- 5-year overall survival, disease free survival and disease specific survival were 57.6%, 52.1%, 68.4% respectively.

## INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) is diagnosed in 1800 patients in England and Wales annually, half of whom have locally advanced disease ((American Joint Committee on Cancer (AJCC 8) stages III and IV) at presentation [1]. Prior to 1991, laryngectomy was considered a treatment of choice offering the highest chance of cure. However, the treatment paradigm shifted towards non-surgical laryngeal preservation strategies following the results of the Veterans Affairs (VA) Laryngeal Cancer Study, which demonstrated equitable survival and favourable laryngeal preservation rates (64%) in patients undergoing induction chemotherapy and definitive radiotherapy versus total laryngectomy and postoperative radiotherapy[2]. The role of concurrent chemoradiotherapy (CRT) was established by the Radiation Therapy Oncology Group 91-11 trial which showed improved locoregional control and even higher laryngeal preservation rates of 81% with concomitant CRT when compared with 67% in the induction chemotherapy/radiation arm and 63% in definitive radiotherapy arm [3].

Whilst primary CRT has become the standard of care for T3 and low-volume T4 disease in most United

States and UK centres since the publication of these two seminal trials, a number of questions regarding the role of larynx preserving strategies remain [4]. In particular, the vexed issue of what constitutes meaningful laryngeal preservation when accounting for function and quality of life. (C)RT is associated with significant side-effects with a third of patients experiencing grade 3-5 toxicities, most notably airway and swallowing ramifications[3]. It is, therefore, of significant clinical relevance to attempt to inform patient selection for these treatment strategies.

## Objectives

We primarily sought to identify the predictive factors for a non-functional larynx in patients with locally advanced LSCC following definitive (chemo)radiotherapy. As a secondary objective, the determinants of locoregional recurrence were investigated.

## METHODS

### Ethical considerations and governance protocols

The project was registered as a service evaluation (10306) and approved by the local clinical governance committee.

### The definition of non-functional larynx

Patients were deemed to have non-functional larynx (NFL) if one of the following criteria were met: 1) gastrostomy dependence >2 years since treatment 2) permanent tracheostomy 3) functional laryngectomy and/or 4) chronic aspiration (defined as the presence of aspiration on videofluoroscopy or fiberoptic endoscopic evaluation of swallow with associated recurrent chest infections).

### Reporting guideline

The manuscript was prepared in accordance to the STROBE guidance.

### Study design and setting

This was a retrospective case-control study conducted in a single tertiary oncology unit. All participants were followed up as per the local head and neck cancer surveillance guidelines.

### Participants and data sources

Eligible consecutive patients were identified from a regional head and neck cancer database (SOMERSET), who had a histological diagnosis of locally advanced (AJCC 8 T3 or T4) laryngeal squamous cell carcinoma (ICD-10 C32.9) and underwent definitive either radiotherapy or chemoradiotherapy with curative intent between 2008 and 2018 at a tertiary head and neck centre. Patients received radiotherapy at a dose of 65-70Gy over 30-35 fractions with or without concurrent cisplatin chemotherapy delivered at either 3- or 4-week intervals at a dose of 100mg/m<sup>2</sup>. All patients were discussed in the regional multidisciplinary team meeting before commencement of treatment. Demographic, clinical and radiological characteristics (cartilage involvement, pre-epiglottic extension) were extracted from the electronic medical records.

### Exclusion criteria

Patients with the following characteristics were excluded from the study: early T stage (T1-2), primary surgical treatment (e.g. laryngectomy, transoral resection), distant metastases at presentation, palliative-intent treatment, synchronous primary tumour in the upper aerodigestive tract and missing medical records.

### Outcome measure

The primary outcome was the NFL rate. The secondary outcomes were overall survival (OS), disease specific survival (DSS), disease free survival (DFS) and locoregional control (LRC) at 5 years.

### Statistical analysis

The data analysis was conducted using SPSS, version 22.0 (Armonk, NY). Exploratory binomial logistic univariate analyses were performed to identify the potential predictors of NFL (age, smoking, T stage, pre-treatment hemi-laryngeal fixation, pre-treatment gastrostomy, chemoradiotherapy (CRT), pre-epiglottic tissue involvement, pre-treatment tracheostomy, outer cartilage cortex breach). To account for multicollinearity of the predictors, a multivariate binary logistic (backward elimination) regression model was performed. Survival analyses were conducted using the Kaplan-Meier curves. The Cox-proportional hazard model was used to determine the significance of the individual factors in predicting the locoregional recurrence. The significance alpha level was set at  $p < 0.05$ .

## RESULTS

### Demographic and clinical characteristics

A total of 94 patients were included in the study. Table 1 summarises the demographic and clinical characteristics. Seventy-five (80%) patients had T3 disease. CRT was administered in 36 (39%) patients.

### Causes of non-functional larynx

NFL occurred in 29 (30.9%) patients due to the following criteria: gastrostomy dependence ( $n=21$ ), permanent tracheostomy ( $n=6$ ), functional laryngectomy due to chondroradionecrosis ( $n=1$ ) and chronic aspiration ( $n=13$ ).

### Regression analyses

Table 2 displays the results of the univariate logistic regression analyses. Current smoking was found to significantly increase the risk of NFL (odds ratio (OR) 4.7, Confidence Interval (CI) 1.7-13,  $p=0.003$ ). A multivariate binary logistic regression using backward elimination method did not identify any other significant variables while current smoking was confirmed to be a strong predictor of NFL (OR 6.8, CI 2.1-22.3,  $p<0.001$ ).

### Oncologic outcomes

Thirty-one patients (32.9%) developed recurrence: 29 patients had loco-regional recurrence 7 of whom had also distant metastases. Two patient presented with distant metastasis only. Salvage laryngectomy was performed in 9 patients due to recurrence. OS, DFS, DSS at 5 years were 57.6%, 52.1%, 68.4% respectively (Figure 1). A 5-year locoregional control was achieved in 69.1%. Pre-treatment hemi-larynx fixation was found to be associated with a significantly increased risk of locoregional recurrence (hazard ratio (HR) 3.4, CI 1.4-8.4,  $p=0.007$ ) (Figure 1).

## DISCUSSION

### Synopsis of key findings

The present study found that 30.9% of patients develop functional failure following (chemo)radiotherapy for locally advanced LSCC. The multivariate analyses demonstrated that the current smokers were 6.8 times more likely to experience functional failure, while hemi-laryngeal fixation conferred a significantly increased risk of loco-regional recurrence (HR 3.4, 95% CI 1.4-8.4,  $p=0.007$ ).

### Study limitations and strengths

Selection bias inherent to a retrospective design notwithstanding, we recognise that the principal limitation of our study relates to a relatively small sample size and, by extension, limited number of NFL events to analyse and to analyse subgroups (e.g. T stage). Not only does this carry a propensity for type I or II statistical error, but also restricted the number of predictive factors that could be examined. This was compounded by use of relatively crude outcome measures, with no availability of patient-reported functional outcome measures, leading potentially to a lack of data granularity. Nevertheless, our study included a homogenous group of patients with locally advanced LSCC for whom robust follow-up data was collated.

Furthermore, as outlined previously we believe this study attempts to enrich the evidence-base around an important clinical question, currently informed by a paucity of data.

### Comparison with other studies and clinical applicability

The literature on the functional failure following primary (C)RT for advanced laryngeal cancer is scarce and oftentimes conflicting. This is partly explained by the lack of consensus on the definition of functional laryngeal failure. Earlier studies have focused on salvage laryngectomy as the key outcome, however more recent studies have emphasised the importance of accounting for all types of laryngeal dysfunction while assessing the effects of organ preservation therapies[5][6]. Our definition is based on those reported in previous studies and addresses key aspects of the laryngeal functions (airway patency, airway protection and swallow)[5]. Dysphonia was not included in the definition as the majority of the patients had vocal complaints. Over 30% of the subjects were found to have NFL in the present study, underlining the importance of careful patient counselling about the expectations of treatment. This figure is higher compared to the study by Heukelom et al. which found 21% develop NFL following (C)RT, which might be explained by a high proportion of non-laryngeal cancers and early stage (T1-T2) tumours included in that study[5].

The identification of factors associated with poor laryngeal function following CRT has been a subject of several studies, however the findings have been far from consistent[5][6]. Smoking has been found to be strongly associated with worse functional outcomes in several studies, which is echoed by our results[5][7]. Likewise, vocal cord fixation was identified to carry a significantly increased risk of locoregional failure and while CRT is still often employed is considered by many to be a marker of poor outcome[8][9]. Conversely, other factors including T stage, nodal status and pre-epiglottic extension were not found to be of a useful predictive value. This has also been shown to be of variable importance in the published literature[10][6].

### CONCLUSION

Laryngeal function failure following (C)RT affects a considerable proportion of patients and smokers appear to be at a significantly increased risk. Large-scale multi-centre studies will likely be required to more accurately identify risk factors, and aid in development of an NFL risk prediction tool. The addition of quantitative data including molecular subclassification and radiomics to enrich this dataset may provide significant predictive and prognostic input into future clinical decision-making.

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## Figures

**Figure 1** . 5-year survival curves for (A) overall survival (57.6%), (B) disease specific survival (68.4%), (C) disease free survival (52.1%) and (D) locoregional control (69.1%). 5-year locoregional control in patients with hemi-larynx fixation was 58.9% compared to 84.2% those without ( $p < 0.001$ ) (E).

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Table 2.docx available at <https://authorea.com/users/385526/articles/581378-predictors-of-non-functional-larynx-following-chemo-radiotherapy-for-locally-advanced-laryngeal-cancer>

